UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/090,458	03/01/2002	Hongyun Chen	100103.403	3348

500 7590 05/17/2004

SEED INTELLECTUAL PROPERTY LAW GROUP PLLC
701 FIFTH AVE
SUITE 6300
SEATTLE, WA 98104-7092

EXAMINER	
QIAN, CELINE X	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 05/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/090,458	CHEN ET AL.	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *12-25,27 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 26* is/are rejected.

7)☒ Claim(s) *1-11 and 26* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/9/02,8/20/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-28 are pending in the application.

Election/Restrictions

Applicant's election with traverse of Group I and SEQ ID NO:4, in the response filed on 2/26/04 is acknowledged. The traversal is on the ground(s) that the invention of Group X should be rejoined with Group I because there is no search burden to search both groups. Applicants argue that a search for the claimed nucleic acid molecules encoding ABCA5 polypeptides would be expected to yield any references that have relevance to complementary, or antisense sequences. Applicants also argue that the nucleic acid molecules having the nucleotide sequences set forth in SEQ ID NO:1, 3, 4 are related sequences. Applicants indicate that the nucleic acid of SEQ ID NO:4 encodes the ABCA5 polypeptide comprising the sequence of SEQ ID NO:5, the nucleotide sequence of SEQ ID NO:3 represents the coding region of SEQ ID NO:1, thus both encodes the ABCA5 polypeptide having sequence of SEQ ID NO:2. Applicants thus conclude that a search of SEQ ID NO:4 would be expected to yield any references having relevance to SEQ ID NO:1 or 3. As such, there is no search burden to search all the sequences.

These arguments are not found persuasive for following reasons. The invention of Group I and X are patentably distinct because they are drawn to compositions that are not related. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the invention of Group X is drawn to a composition comprising a pharmaceutically effective amount of an antisense oligonucleotide of SEQ ID NO:1, 3 or 4. The antisense oligonucleotide has different function and effect than the

nucleic acid molecule of Group I, especially as a pharmaceutical composition. Overexpression of the nucleic acid of Group I vs. inhibiting expression of the nucleic acid of Group I (using the antisense oligonucleotide of Group X) achieves different purposes, and maybe used to treat different diseases. Furthermore, the antisense oligonucleotide of Group X has a different classification than the nucleic acid molecules of Group I. A search of Group I is not co-extensive with a search of Group X. Therefore, it would have been burdensome to search both groups in a single application.

Applicants have elected SEQ ID NO:4 for examination. Although the specification discloses that SEQ ID NO:4 encodes ABCA5 polypeptide represented by SEQ ID NO:5, whereas SEQ ID NO:1or 3 encodes ABCA5 polypeptide represented by SEQ ID NO:2, the relationship between SEQ ID NO:4 and SEQ ID 1 or 3 is still unclear. SEQ ID NO:2 and SEQ ID NO:5 are polypeptides with different amino acid sequences. They may have the same name, ABCA5, however, they are still patentably distinct inventions because they may encode proteins of different functions. Nucleic acid molecules encoding different proteins are patentably distinct from each other. Therefore, a search of all the sequences is not co-extensive and would be burdensome. In addition, as discussed in the restriction requirement mailed on 1/29/04, this restriction to examination of a single sequence is due to the now very high and undue burden for examining more than one sequence which is caused by the continued exponential increase of size of the sequence databases to be searched for each sequence, resulting in a corresponding increase in computer search time and examiner time for reviewing the computer search results. Therefore, the limited resources of the Office no longer permit examination of more than one sequence in an

application. As such, the restriction requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 12-25, 27 and 28 are withdrawn from consideration for being directed to non-elected subject matter. Claims 1-11 and 26 are currently under examination.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. For example, see page 17, line 10, and page 30, line 5 and 24. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Objections

Claims 1-11 and 26 are objected to for containing non-elected subject matter. The claims recite nucleic acids represented by sequences of a number of SEQ IDs, however, Applicant has elected SEQ ID NO:4 for examination. Amending the claims such that they are only directed to elected inventions is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-11 and 26 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

The claims are drawn to an isolated nucleic acid molecule encoding an ABCA5 transporter, functional fragment, allelic variant, its complementary sequence, a pharmaceutical

composition comprising said nucleic acid molecule, a vector comprising said nucleic acid encoding an ABCA5 transporter, a host cell comprising said vector, and a method of producing a polypeptide by culturing said host cell. The claims are further drawn to a primer that comprises 12 contiguous nucleotides of SEQ ID NO:4, a nucleic acid molecule comprising the sequences encoding an ABCA5 transporter and another polypeptide.

Before the utility of a nucleic acid molecule comprising the nucleotide sequence which encodes the ABCA5 transporter of SEQ ID NO: 5 can be addressed, the utility of the protein itself must be addressed. Applicants assert that SEQ ID NO: 5 encodes a novel human ABC transporter ABCA5 (see page 14, lines 20-22). Applicants further assert that the nucleic acid and the protein is useful for a) screening assays; b) predictive medicine and c) methods of treatment (see page 55, lines 15-19).

However, based upon applicant's disclosure, the claimed invention does not meet the utility requirement because Applicant has not demonstrated the function of the protein encoded by nucleic acid of SEQ ID NO: 4, or other fragments or variants. In addition, neither Applicants' disclosure nor the state of the prior art at the time the invention was made provides guidance as to whether the protein encoded by nucleic acid sequence of SEQ ID NO: 4 possesses critical structural elements such as the catalytic domain, binding domain, and the like such that one of skilled in the art would accept Applicant's assertions that these molecules possess same functions as other ABC transporter members.

The state of the art suggests that sequence identity alone is insufficient to accurately predict its asserted utility, and that sequence comparison cannot be used solely to determine function. Bork (Genome Research, 10:348-400, 2000) clearly teaches the pitfalls associated with

comparative sequence analysis for predicting protein function because of known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact sequencing itself is highly automated and accurate (page 398, column 1). One of the reasons for this inaccuracy is that the quality of data available is still insufficient. This is particularly true for data relating to protein function. Protein function is context dependent, and both molecular and cellular aspects must be considered (page 398, column 2). Many bioinformatic methods have difficulty exceeding a 70% prediction accuracy. (see page 400, column 1, 2nd paragraph, lines 1-5). In addition, Smith et al (Nature Biotechnology 15:1222-1223, 1997) indicates that there are numerous cases in which proteins of very different function are homologous (page 1222, third column, last paragraph). Furthermore, Brenner (TIG 15:132-133, 1999) teaches the difficulty of accurately infer function from homology, and clearly states that most homologs have different molecular and cellular functions (column 2, second paragraph, page 132). Examples of pitfalls associated with comparative sequence analysis for predicting protein function in enzymes associated with modification of fatty acids are shown by Broun et al. (Science 282:1315-1317, 1998) and Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995). Broun et al. teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydroxylase and as few as six amino acid substitutions can transform a hydroxylase to a desaturase (see abstract). Similarly, Van de Loo et al. teaches that polypeptides of approximately 67% homology to a desaturase from *Arabidopsis* where found to be hydroxylase once tested for activity (see abstract).

Thus, given the limitations and pitfalls of using computational sequence analysis, it is apparent that the biological function of the protein encoded by SEQ ID NO: 4 cannot be

accurately predicted based solely upon sequences similarly with sequence(s) known in the prior art. Although the ABC transporter family members are involved in activities such as transporting neurotoxic molecules, multi-drug resistance and cholesterol efflux, whether the protein encoded by SEQ ID NO: 4 or fragments thereof possess any of such activities is unpredictable.

The specification discloses that the nucleic acid molecules of the invention can be used as primers, probes, or antisense, etc. These utilities are credible, but not substantial or specific because any nucleic acid can be used for such purposes. Further, since the specification does not disclose specific DNA or RNA targets, such utility is not substantial. The specification also discloses using the nucleic acid as pharmaceutical composition. This utility is not substantial or specific because the specification does not identify which disease is associated to the disclosed ABCA5 transporter or its mutant form. Nor does the specification teaches how to treat any diseases with the nucleic acid of the invention (for example, route of administration or effective dosage). As such, such asserted utility cannot be used in a real world sense, and it is not a substantial utility. Moreover, since the polypeptide of SEQ ID NO: 5 lack utility for the reasons set forth above, nucleic acid molecules comprising the nucleotide sequence of SEQ ID NO: 4 that encodes said polypeptide, or a fragment or variant thereof, a vector and a host cell comprising said nucleotide sequences, and a process of making said polypeptide would also lack utility. The art does not teach any well-established utility for the claimed nucleic acid sequences. Therefore, the inventions of claims 1-11 and 26 lack substantial/specific utility or well-established utility.

Claims 1-11 and 26 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

The nature of the invention

The claims are drawn to an isolated nucleic acid molecule encoding an ABCA5 transporter, functional fragment, allelic variant, its complementary sequence, a pharmaceutical composition comprising said nucleic acid molecule, a vector comprising said nucleic acid encoding an ABCA5 transporter, a host cell comprising said vector, and a method of producing a polypeptide by culturing said host cell. The claims are further drawn to a primer that comprises 12 contiguous nucleotides of SEQ ID NO:4, a nucleic acid molecule comprising the sequences encoding an ABCA5 transporter and another polypeptide.

The breadth of the claims

The breadth of the claim is broad. The broadest claim encompasses any isolated nucleic acid molecule that is 90% to a portion of SEQ ID NO:4, that is any nucleic acid molecule(s) share 9 base pair homology with any 10 base pair fragment of SEQ ID NO:4 (5475 bp). Claim 55 encompasses any 12 contiguous oligonucleotide(s) that is homologous with a region of SEQ ID NO:4.

The teaching of the specification and working examples

The specification discloses that the SEQ ID NO:4 encodes a novel ABC transporter family member named ABCA5. The specification further discloses that an ABCA5 transporter is a polypeptide having 50%-97% sequence identity with the full length sequence of human ABCA5 transporter having amino acid sequence of SEQ ID NO:2 or 5 and have at least one of the functional aspects including activation of an ABCA5-dependent signal transduction pathway, modulation of the transport of a substrate, interaction of an ABCA5 protein with a non membrane associated protein, etc (see page 14, lines 3-17). However, the specification does not teach the any ABCA5 transporter or fragment thereof, including the one encoded by SEQ ID NO: 4 has the disclosed functions. The specification also fails to disclose any nucleic acids encoding fusion proteins comprising ABCA5 transporter. The specification does not provide any working example(s) that demonstrates the function of the ABCA5 transporter encoded by the claimed nucleic acid sequences. One of skilled of art would not know how to use these claimed nucleic acid molecules because they lack substantial and specific utility as discussed above. Moreover, the specification does not teach what genetic diseases are associated with the claimed nucleic acid molecules or ABCA5 transporter disclosed by the instant specification. Nor

does the specification teaches how to treat a specific disease by the claimed nucleic acid molecule. Therefore, the skilled artisan would have to rely on the teaching of the prior art to use the claimed inventions.

The state of prior art and the level of predictability in the art

The state of art at the time of filing teaches human ABC transporter family currently comprises 47 members which belong to 7 subfamilies and is steadily growing (see Efferth, 2001, Current Molecular Medicine, Vol 1, page 45, 2nd col., 1st paragraph). Efferth further discussed association between individual member(s) of the ABC transporter and genetic diseases, and perspectives for diagnosis and therapy using these individual members. The mRNA and protein of human ABCA5 is not disclosed in this article, thus there is no information regard the function of this protein or any association between ABCA5 transporter and disease (see table 1). The art is also silent on how to use the claimed nucleic acid molecules that shares sequence homology with SEQ ID NO:4 or fragment thereof. Therefore, the skilled artisan would not know how to use the claimed invention based on the teaching of prior art.

Although the specification discloses SEQ ID NO:4, a nucleic acid encoding a human ABCA5 transporter shares sequence homology with ABC transporter family members, the sequence homology alone cannot predict protein function for reasons discussed in the utility rejection. Therefore, whether the claimed nucleic acid molecules encode ABC transporters that have functions possessed by other ABC transporter member is unpredictable. As such, it is also unclear how to use a nucleic acid encoding a fusion protein of ABCA5 transporter. In addition, since neither the prior art nor the specification teaches an association between the claimed

nucleic acid and genetic diseases, whether the claimed nucleic acids can be used as a pharmaceutical composition is unpredictable.

The quantity of experimentation

The specification fails to teach how to use the claimed nucleic acid for their asserted utility. Absent teaching from the prior art and lack of guidance from the instant specification, one of skilled in the art would have to engage in undue experimentation to use the invention. Therefore, the invention is not enabled by the instant specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 and 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description requirement is set forth by 35 U.S.C. 112, first paragraph which states that the: "*specification* shall contain a written description of the invention. . .[emphasis added]." The written description requirement has been well established and characterized in the case law. A specification must convey to one of skill in the art that "as of the filing date sought, [the inventor] was in possession of the invention." See *Vas Cath v. Mahurkar* 935 F.2d 1555, 1560 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Applicant may show that he is in "possession" of

the invention claimed by describing the invention with all of its claimed limitations "by such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention." See *Lockwood v. American Airlines Inc.* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

In analyzing whether the written description requirement is met, it is first determined whether a representative number of species have been described by their complete structure. Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. The claims recites an isolated nucleic acid encoding functional fragment of an ABCA5 transporter that share 90% homology to a portion of SEQ ID NO:4, 90% to a portion of amino acid sequence of SEQ ID NO:5, or a nucleotide sequence that hybridizes to SEQ ID NO:4. Claim 6 recites an complementary sequence to said sequence, and claim 7 recites a nucleic acid molecule comprising said sequence and a sequence encoding a heterologous polypeptide. This claimed genus potentially encompasses a large number of nucleic acid molecules of various sizes, structures or functions that may not be related. The specification does not teach any function of the full length or fragments of the protein encoded by SEQ ID NO:4. The specification also fails to teach what portion of SEQ ID NO:4 is essential for its function as an ABCA5 transporter. As such, the structural functional relationship is missing. Further, the specification fails to teach any nucleic acid sequences encoding a fusion of ABCA5 and another protein. Therefore, the specification fails to describe a representative number of species by their complete structure or other identifying characteristics, and the written description requirement is not met.

Claim 4 recites naturally occurring allelic variant of the amino acid set forth in SEQ ID NO:5 which is recognized by an antibody selectively bind to the polypeptide of SEQ ID NO:5. The specification fails to disclose any antibody selectively bind to the polypeptide of SEQ ID NO:5, nor does the specification discloses any allelic variants that is recognized by such antibody. As such, the structural requirement of those allelic variants for them to be recognizable by an antibody that binds to the polypeptide of SEQ ID NO:5 is unknown. Claim 5 recites an oligonucleotide primer comprising at least 12 contiguous nucleotides of SEQ ID NO:4 or a complement from a region specific to ABCA5 transporters. The specification fails to disclose which region is specific to ABCA5 transporters that distinguishes it from other ABC transporter or non-transporter proteins. As such, the structurally requirement for the claimed primers is not known. Therefore, the written description requirement is not met.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "producing a polypeptide comprising culturing the host cell of claim 10 in an appropriate culture medium" renders the claim indefinite because it is unclear what polypeptide is being produced. The host cell of claim 10 can produce a wide variety of polypeptide, either endogenous polypeptide of any kind, or the recombinant polypeptide expressed by the expression vector. As such, the culture condition is largely dependent on what

polypeptide would be produced. The claim is indefinite because the metes and bounds of the polypeptide and the "appropriate culture medium" cannot be established.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 5 and 6 are rejected under 35 U.S.C. 102(a) as being anticipated by the nucleotide sequence having the accession number BG149983.

The claims are drawn to an isolated nucleic acid molecule which is 90% identical to a portion of the nucleotide sequence of SEQ ID NO:4. Since the size of the portion is not defined, such nucleic acid molecule can be any nucleotide that share as little as 9bp homology with a portion of 10bp of SEQ ID NO:4, and a complementary strand thereof. Claim 12 is drawn to a oligonucleotide that comprising at least 12 contiguous nucleotides of SEQ ID NO:4.

The nucleotide sequence having the accession number BG149983 share more than 500bp homology with SEQ ID NO:4. Therefore, it anticipates the claimed inventions.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Celine Qian, Ph.D.